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IMPAX LABORATORIES, INC.

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

SAN FRANCISCO DIVISION

EMC

IMPAX LABORATORIES, INC.,

Plaintiff,

v.

MEDICIS PHARMACEUTICAL CORP.,

Defendant.

CASE NO.: CV 08 0253

COMPLAINT FOR DECLARATORY JUDGMENT

Plaintiff IMPAX Laboratories, Inc. ("IMPAX"), for its Complaint, avers as follows:

PARTIES

1. IMPAX is a corporation organized under the laws of the State of Delaware, with its principal place of business in Hayward, California.

2. Upon information and belief, defendant Medicis Pharmaceutical Corp. ("Medicis") is a corporation organized under the laws of the State of Delaware, with its principal place of business in Scottsdale, Arizona.

JURISDICTION AND VENUE

3. This action arises under the Declaratory Judgment Act, Title 28 of the United States Code, Chapter 151, for the purpose of determining an actual and justiciable controversy

between the parties hereto. This Court has subject matter jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1338(a). Venue is proper in this judicial district pursuant to 28 U.S.C. § 1391(b).

INTRADISTRICT ASSIGNMENT

4. Pursuant to Civil Local Rule 3-2(c), this action is to be assigned on a district-wide basis.

CLAIM FOR RELIEF

5. U.S. Patent No. 5,908,838 ("the '838 patent"), entitled "Method for the treatment of acne," was issued by the United States Patent and Trademark Office on June 1, 1999. A copy of the '838 patent is attached hereto as Exhibit A.

6. Medicis is the named assignee of the '838 patent.

7. IMPAX submitted an Abbreviated New Drug Application ("ANDA") under section 505(j) of the Federal Food, Drug, and Cosmetic Act, in order to obtain approval to commercially manufacture and sell minocycline hydrochloride extended release tablets, a generic version of SOLODYN™ extended release tablets.

8. The drugs for which IMPAX seeks approval have the same active ingredient, route of administration, dosage form, and strength as SOLODYN™ extended release tablets.

9. Medicis claims that the use of SOLODYN™ is covered by one or more claims of the '838 patent.

10. Medicis asserts that generic competitors to SOLODYN™ face the risk of a suit for infringement of the '838 patent.

11. Medicis states that it intends to aggressively and vigorously enforce the '838 patent against generic competitors to SOLODYN™.

12. By a letter dated December 20, 2007, IMPAX, through its counsel, informed Medicis that IMPAX submitted an ANDA in order to obtain approval to commercially manufacture and sell minocycline hydrochloride extended release tablets, offered to provide access to relevant portions of the ANDA, and requested Medicis to provide IMPAX with a covenant not to sue under the '838 patent. Medicis has not provided the requested covenant not to sue.

13. The '838 patent is invalid for failure to satisfy the requirements of Part II of Title 35 of the United States Code, including without limitation one or more of 35 U.S.C. §§ 101, 102, 103 and 112.

14. IMPAX does not infringe any valid claim of the '838 patent.

15. As a result of Medicis' acts and omissions, an actual and justiciable controversy exists between IMPAX and Medicis with respect to whether IMPAX infringes any valid claim of the '838 patent.

PRAYER

WHEREFORE, IMPAX prays for a judgment that:

A. Declares that the claims of the '838 patent are invalid;

B. Declares that IMPAX does not infringe any valid claim of the '838 patent;

C. Awards IMPAX its costs and attorneys' fees; and

D. Awards IMPAX such other and further relief as the Court may deem proper.

CERTIFICATION OF INTERESTED ENTITIES OR PERSONS

Pursuant to Civil Local Rule 3-16, the undersigned certifies that as of this date, other than the named parties, there is no such interest to report

Dated: January 15, 2008

WILSON SONSINI GOODRICH & ROSATI
Professional Corporation

By: _____
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Attorneys for Plaintiff
IMPAX LABORATORIES, INC.

US005908838A

United States Patent [19]

Gans

[11] Patent Number: 5,908,838

[45] Date of Patent: Jun. 1, 1999

[54] METHOD FOR THE TREATMENT OF ACNE

[75] Inventor: **Eugene H. Gans**, Phoenix, Ariz.

[73] Assignee: **Medics Pharmaceutical Corporation**, Phoenix, Ariz.

[21] Appl. No.: **09/028,871**

[22] Filed: **Feb. 19, 1998**

[51] **Int. Cl.**[6] **A61K 31/65**

[52] **U.S. Cl.** **514/152**

[58] **Field of Search** 514/152

[56] **References Cited**

U.S. PATENT DOCUMENTS

5,518,730 5/1996 Fuisz 424/426

OTHER PUBLICATIONS

Williams et al., the Lancet, 2(7883) 744–6 Sep. 28, 1974.

Primary Examiner—Phyllis Spivack
Attorney, Agent, or Firm—William J. McNichol, Jr.

[57] **ABSTRACT**

A method for the treatment of acne is provided which results in the reduction of vestibular side effects following administration of oral tetracycline antibiotics.

18 Claims, No Drawings

METHOD FOR THE TREATMENT OF ACNE

FIELD OF THE INVENTION

This invention relates to methods for the treatment of acne, and in particular to methods for the treatment of acne involving the use of oral tetracycline antibiotics.

BACKGROUND OF THE INVENTION

Oral tetracycline antibiotics are frequently used in the treatment of acne. One of the most effective oral tetracycline antibiotics used in the treatment of acne it is minocycline. All tetracycline antibiotics are known to have some side effects. These side effects include vestibular symptoms such as vertigo, dizziness or blurred vision. These effects are sometimes disabling. See, Gould & Brookler, Arch. Otolarang. Vol. 96, p. 291 (1972); Williams et al., Lancet, Sep. 28, 1974, p. 144–45; Fanning & Gump, Arch. Intern. Med., Vol. 136, pp. 761–62 (1976). Headache and general malaise, along with gastro-intestinal symptoms such as the diarrhea, nausea, gas, or cramps also occur. Dry nose and dry mouth are also occasionally encountered.

Dosage forms of oral tetracycline antibiotics are typically constructed with a view towards achieving rapid dissolution rates. Rapid dissolution is believed to be essential to the effectiveness of these drugs. The driving force behind this practice is the understanding that rapid dissolution leads to rapid assimilation through the gut lining, where the antibiotics are then transmitted through the blood stream to the skin, where they are active against bacteria associated with acne. The U.S. Food and Drug Administration (FDA) has established standards for dissolution rates for various oral antibiotics. These standards set minimum dissolution rates. For example, the FDA standard for oral minocycline is that 75 percent of the stated dosage must have dissolved within 45 minutes, under standard U.S. Pharmacopea test conditions. Commercial products are typically engineered to have a dissolution rates which are substantially faster than that required by the FDA. All of this is based upon the generally accepted belief in the art that, while dissolution rates enhance the effectiveness of the antibiotic, once the FDA minimum dissolution rate is achieved, all products have equivalent safety and efficacy.

SUMMARY OF THE INVENTION

It has been discovered that the dissolution rate of oral tetracycline antibiotics, especially minocycline, can affect the occurrence of vestibular side effects. Specifically, too rapid dissolution of oral tetracyclines increases the incidence and severity of vestibular side effects. By reducing or slowing the dissolution rates of the antibiotics, the incidence and/or severity of vestibular side effects can be reduced significantly.

DETAILED DESCRIPTION OF THE INVENTION

Vestibular reactions are an undesirable and sometimes seriously disconcerting side effect of minocycline therapy. According to the present invention, it is possible to provide persons susceptible to such side effects with the benefits of minocycline therapy while diminishing the incidence and/or severity of these side effects. This is accomplished by adjusting the dissolution rate of the minocycline in its dosage form so that, while an effective concentration of minocycline is achieved in the blood stream of the patient, vestibular side effects are greatly reduced.

In a preferred embodiment of the invention, the minocycline dissolves at a rate of only 15 percent within the first 15 minutes, 35 percent within 30 minutes, 50 percent within 45 minutes, and 80 percent within one hour. It is also advantageous to use a dissolution rate of 20 percent within 15 minutes, 50 percent in 30 minutes, 75 percent within 45 minutes and 100 percent dissolution within 60 minutes. Dissolution rates as fast as 30 percent within 15 minutes, 60 percent within 30 minutes, 75 percent within 45 minutes and complete dissolution within 60 minutes or even as fast as 35 percent within 15 minutes, 80 percent within 30 minutes and substantially complete dissolution within 45 minutes can be used. Preferred dissolution rates are within the range of 20 to 40 percent in 15 minutes, 50 to 80 percent in 30 minutes, and 70 to 95 percent in 45 minutes. Faster rates of 25 to 35 percent in 15 minutes, 60 to 80 percent in 30 minutes and 80 to 100 percent in 45 minutes are useful. It will be understood however, that the faster dissolution rates do not achieve as significant a reduction in the reduction of unwanted side effects as the slower dissolution rates.

Minocycline is available from a variety of sources. Various commercial products containing minocycline as their active ingredient have a variety of the dissolution rates. In the following example, slower dissolving minocycline is compared with fast-dissolving minocycline.

A blinded cross-over study of the vestibular side effects of minocycline involving 32 female subjects was conducted. The subjects were given either a fast dissolving or a slower dissolving dosage form of minocycline. The doses for the subjects were adjusted on the basis of each subject's total body weight and were in the range typically used for the treatment of severe acne. Subjects weighing 50 to 69 kg were given one-hundred milligrams. Subjects weighing 70 to 89 kg, the dose were given one hundred fifty milligrams and subjects above received 90 kilograms, 200 milligrams. This dose was given once a day at 5 p.m. Subjects received one of the two dose forms for four days. After a two week washout, each group "crossed over" and received the dosage form that they had not received during the first four day period. Each subject was required to maintain an accurate diary of vestibular side effects. The diary recorded the number of days that each subject experienced vestibular side effects and the number of incidents of each symptom. The 32 subjects were evaluated over a five day period, yielding 160 person-day measurements per treatment group. The number of days that each subject recorded a side effect and the severity of that side effect the reported in Table 1.

From Table 1 it can be seen that a total of 27 incidents of vestibular side effects occurred in the fast dissolving treatment group, compared to only five incidents in the slower dissolving group. The severity of the vestibular side effects are reported on a scale of 1 to 4. With 1 indicating slight severity, 2 indicating mild severity, 3 moderate, and 4 severe side effects.

The dissolution rates for the fast dissolving dosage form and the slower dissolving dosage form are set forth below.

TABLE 1

	Vestibular Side Effects			
Symptom	Severity	No. of Time Intervals	Duration	Severity Category
Patients Treated With Slower-Dissolving Minocycline				
dizziness	slight	2	8:00 am–4:00 pm	1
dizziness	slight-mild	4	all day	1.5
dizziness	mild	1	on and off	2
dizziness	slight	1	all evening	1

TABLE 1-continued

Vestibular Side Effects				
Symptom	Severity	No. of Time Intervals	Duration	Severity Category
dizziness	slight-mild	2	morning thru mid day	1.5
Patients Treated With Fast-Dissolving Minocycline				
dizziness	slight	2	7:00 am–12:00 pm	1
blurred vision	slight-mild	2	8:00 am–3:00 pm	1.5
dizziness	slight	2	7:00 am–12:00 pm	1
dizziness	slight	2	8:00 am–2:00 pm	1
dizziness	slight	2	7:00 am–2:00 pm	1
dizziness	slight	2	7:00 am–3:00 pm	1
dizziness	slight	2	morning-late afternoon	1
dizziness	slight	2	morning-late afternoon	1
dizziness	slight	2	morning-late afternoon	1
dizziness	slight	1	1 hour	1
dizziness	slight	1	2 hours	1
dizziness	slight	1	about 1–2 hours	1
dizziness	slight	1	about 1.5 hours	1
dizziness	slight	1	2 hours	1
blurred vision	slight	1	1 hour	1
dizziness	slight	1	2 hours	1
dizziness	slight-mild	2	7.5 hours	1.5
dizziness	mild	1	6:00 am–8:00 am	2
vertigo	mild	1	2:00 am–8:00 am	2
dizziness	mild	1	6:00 am–8:00 am	2
vertigo	mild	1	2:00 am–8:00 am	2
dizziness	mild	1	6:00 am–8:00 am	2
vertigo	mild	1	6:00 am–8:00 am	2
dizziness	mild	1	6:00 am–8:00 am	2
vertigo	mild	1	6:00 am–8:00 am	2
dizziness	mild	1	6:00 am–8:00 am	2
vertigo	mild	1	6:00 am–8:00 am	2

TABLE 2

Fast Dissolving		Slow Dissolving	
Time (Min.)	% Dissolution	Time (Min.)	% Dissolution
0	0.0	0	0.0
15	100	15	30
30	100	30	67
45	100	45	88
60	100	60	95

The cause of the effectiveness of this invention is not known. However, it can be speculated that the dissolution rates called for by the present invention allow the vestibular organs to acclimate themselves to the presence of the minocycline, and thereby avoid unwanted side effects. This explanation is consistent with the avoidance of vestibular side effects even through the use of both slow and fast dissolving dosage forms may achieve the same level of minocycline in the blood stream.

The foregoing example is given by way of illustration only. The scope of the invention is defined only by the following claims.

I claim:

1. A method for reducing the incidence or severity of vestibular side effects resulting from the treatment of acne by the use of oral tetracycline antibiotics, comprising administering the oral tetracycline antibiotic in a slowly dissolving dosage form.

2. The method of claim **1**, wherein the oral tetracycline antibiotic is minocycline.

3. The method of claim **2**, wherein the antibiotic dissolves at a rate no faster than 15 percent in 15 minutes, 35 percent in 30 minutes, 50 percent in 45 minutes and 80 percent in 60 minutes.

4. The method of the claim **2** wherein the antibiotic dissolves at a rate no faster than 20 percent in 15 minutes, 50 percent in 30 minutes, and 75 percent in 45 minutes.

5. The method of claim **2** wherein and the antibiotic dissolves at a rate no faster than 30 percent in 15 minutes, 60 percent in 30 minutes, and 75 percent in 45 minutes.

6. The method of the claim **2** wherein the antibiotic dissolves at a rate no faster than 35 percent in 15 minutes, 80 percent in 30 minutes, and one hundred percent in 45 minutes.

7. The method of claim **2**, wherein the antibiotic dissolves at a rate within the range of 20 to 40 percent in 15 minutes, 50 to 80 percent in 30 minutes, 70 to 95 percent in 45 minutes and 95 to 100 percent in 60 minutes.

8. The method of the claim **2** wherein the antibiotic dissolves at a rate within the range of 25 to 35 percent in 15 minutes, 60 to 80 percent in 30 minutes, and 80 to 100 percent in 45 minutes.

9. The method of claim **2** wherein and the antibiotic dissolves at a rate within the range of 30 to 35 percent in 15 minutes, 65 to 75 percent in 30 minutes, and 90 to 100 percent in 45 minutes.

10. A method for reducing the incidence or severity of vestibular side effects resulting from the treatment of acne by the use of oral tetracycline antibiotics, comprising administering the oral tetracycline antibiotic in a slowly dissolving dosage form, wherein the dissolution of the antibiotic is substantially complete in less than 24 hours.

11. The method of claim **10**, wherein the oral tetracycline antibiotic is minocycline.

12. The method of claim **11**, wherein the antibiotic dissolves at a rate no faster than 15 percent in 15 minutes, 35 percent in 30 minutes, 50 percent in 45 minutes and 80 percent in 60 minutes.

13. The method of the claim **11** wherein the antibiotic dissolves at a rate no faster than 20 percent in 15 minutes, 50 percent in 30 minutes, and 75 percent in 45 minutes.

14. The method of claim **11** wherein and the antibiotic dissolves at a rate no faster than 30 percent in 15 minutes, 60 percent in 30 minutes, and 75 percent in 45 minutes.

15. The method of the claim **11** wherein the antibiotic dissolves at a rate no faster than 35 percent in 15 minutes, 80 percent in 30 minutes, and one hundred percent in 45 minutes.

16. The method of claim **11**, wherein the antibiotic dissolves at a rate within the range of 20 to 40 percent in 15 minutes, 50 to 80 percent in 30 minutes, 70 to 95 percent in 45 minutes and 95 to 100 percent in 60 minutes.

17. The method of the claim **11** wherein the antibiotic dissolves at a rate within the range of 25 to 35 percent in 15 minutes, 60 to 80 percent in 30 minutes, and 80 to 100 percent in 45 minutes.

18. The method of claim **11** wherein and the antibiotic dissolves at a rate within the range of 30 to 35 percent in 15 minutes, 65 to 75 percent in 30 minutes, and 90 to 100 percent in 45 minutes.

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